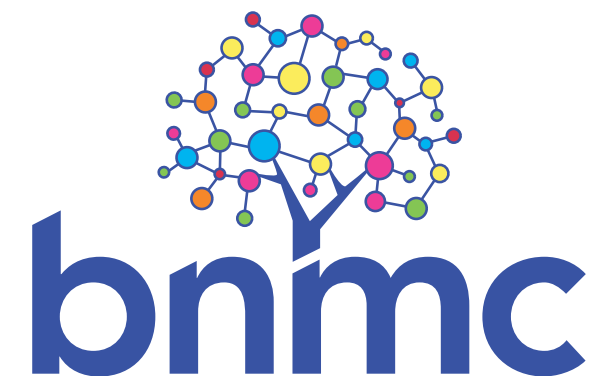


SBML, BioModels.net, and SBGN

Michael Hucka

*Co-director—Biological Network Modeling Center (BNMC), Beckman Institute
Senior Research Fellow—Control and Dynamical Systems*

*California Institute of Technology
Pasadena, California, USA*



SBML background

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- ▶ Conviction that computational modeling becoming crucial
 - ▶ Mechanistic modeling and dynamical simulation enables **quantitative hypothesis testing**

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 - ▶ Mechanistic modeling and dynamical simulation enables **quantitative hypothesis testing**
- ▶ Not a new idea—dates to 1940's if not earlier

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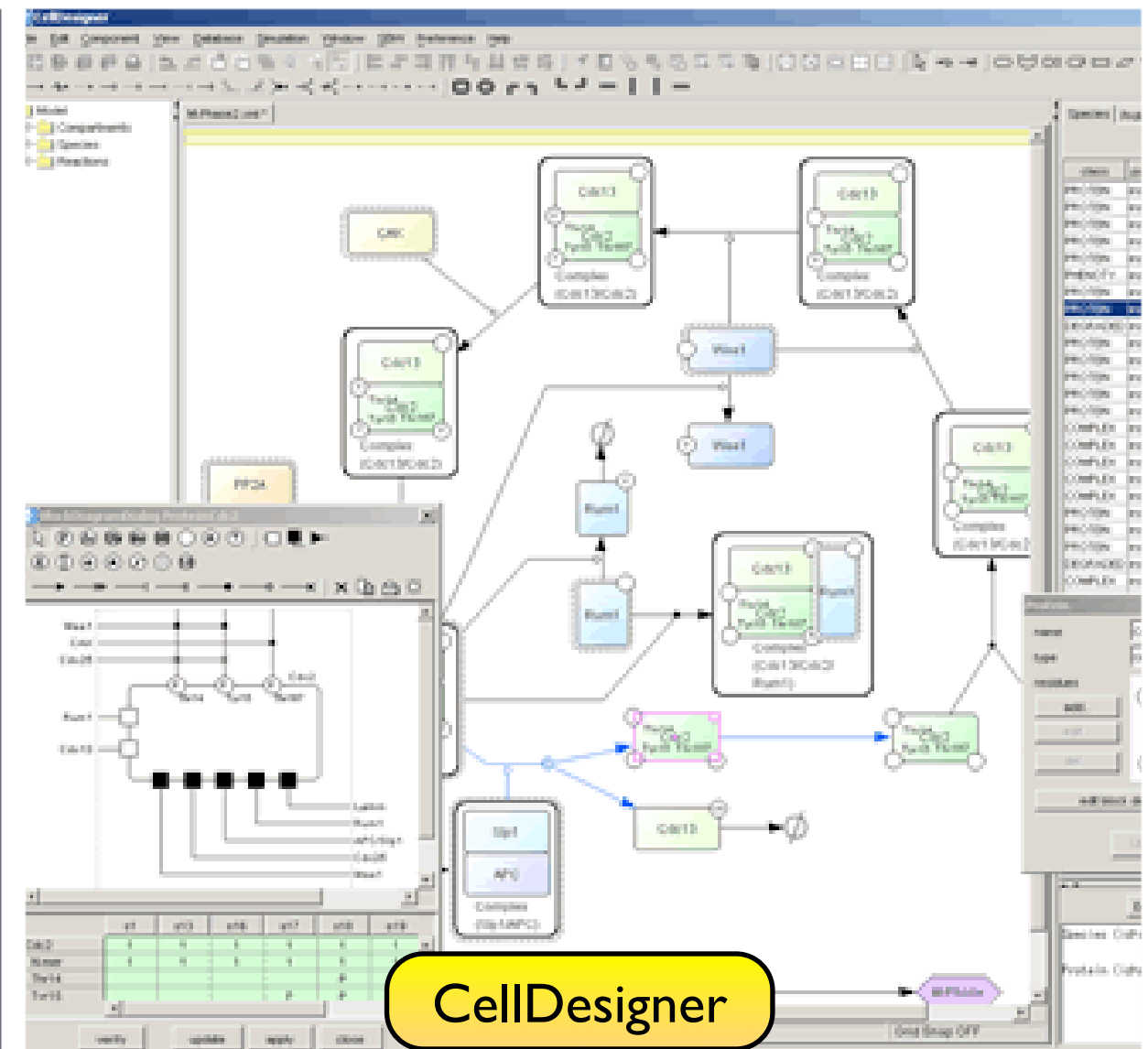
- ▶ Conviction that computational modeling becoming crucial
 - ▶ Mechanistic modeling and dynamical simulation enables **quantitative hypothesis testing**
- ▶ Not a new idea—dates to 1940's if not earlier
- ▶ Today software tool support is better than ever

Specialized software tools for computational modeling in biology

- ▶ > 100 available
- ▶ Range of capabilities
 - ▶ Editing/creating models
 - ▶ Simulating/analyzing
 - ▶ Visualizing
 - ▶ Databasing

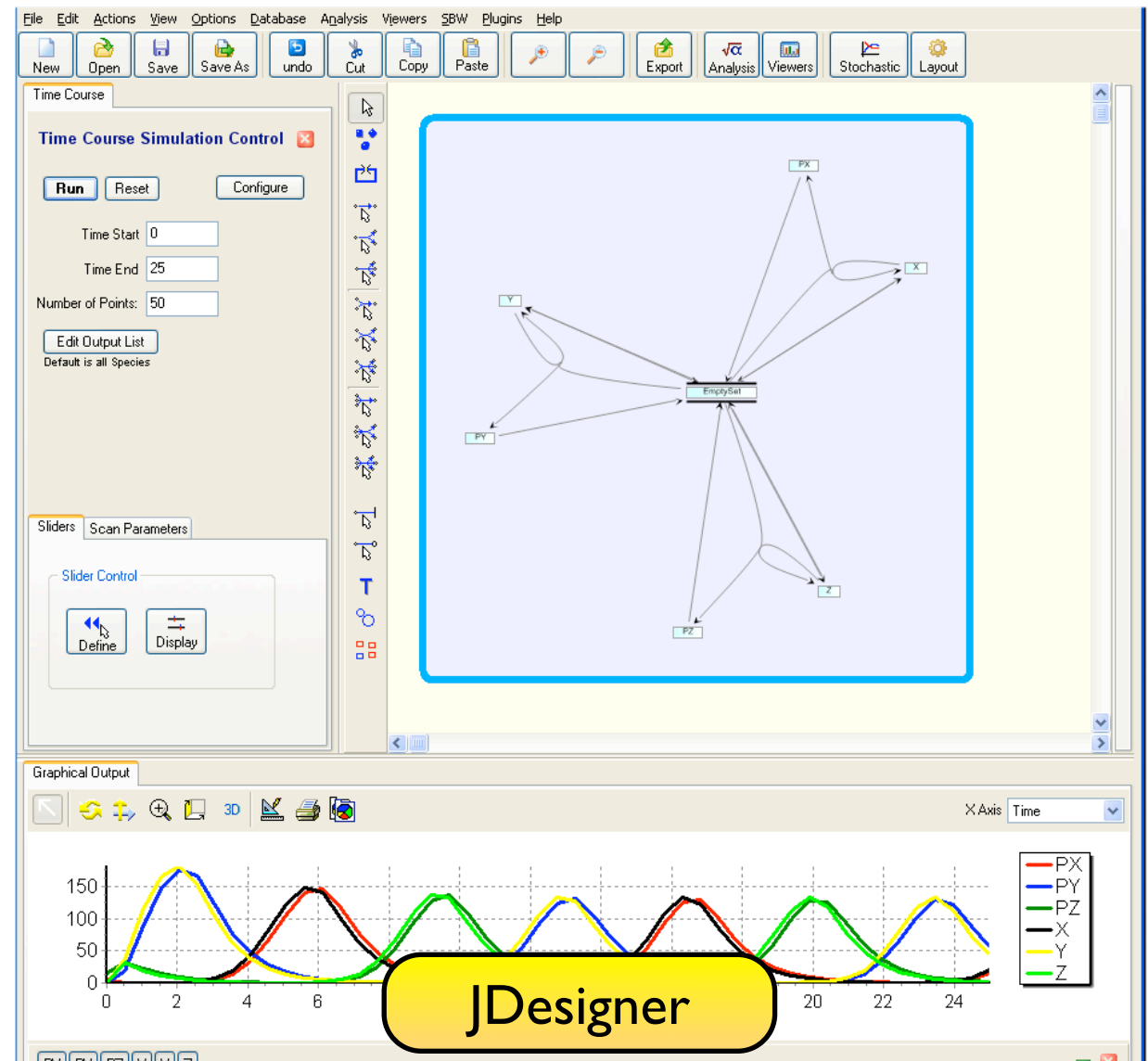
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COPASI (4.0 Build 8)

The screenshot displays the COPASI software interface. On the left is a hierarchical tree view under the 'Copasi' root, with categories like Model, Biochemical, Mathematical, Tasks, Multiple Tasks, Output, Functions, and Preferences. The 'Reactions' sub-item under 'Biochemical' is selected. The main window on the right shows a table of reactions with columns for Name and Equation.

| | Name | Equation |
|----|------------------|------------------------------------|
| 1 | HXT | GLCo = GLCi |
| 2 | HK | GLCi + ATP = G6P + ADP |
| 3 | PGI | G6P = F6P |
| 4 | PFK | F6P + ATP -> F16bP + ADP; AMP F26 |
| 5 | ALD | F16bP = DHAP + GAP |
| 6 | TPI | DHAP = GAP |
| 7 | GAPDH | GAP + NAD = BPG + NADH |
| 8 | PGK | BPG + ADP = P3G + ATP |
| 9 | PGM | P3G = P2G |
| 10 | ENO | P2G = PEP |
| 11 | PYK | PEP + ADP = PYR + ATP |
| 12 | PDC | PYR -> AcAld + CO2 |
| 13 | ADH | EtOH + NAD = AcAld + NADH |
| 14 | ATPase | ATP -> ADP |
| 15 | AK | 2 * ADP = ATP + AMP |
| 16 | G3PDH | DHAP + NADH -> Glycerol + NAD |
| 17 | Glycogen Branch | G6P + ATP -> ADP + Glycogen |
| 18 | Trehalose Branch | 2 * G6P + ATP -> ADP + Trehalose |
| 19 | Succinate Branch | 2 * AcAld + 3 * NAD -> Succinate + |
| 20 | | |

COPASI

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| Reaction | Name | Type | |
|-------------|---|------------------|----------------------|
| Ma->Mi | MPF inactivation | Mass Action | kw*Ma |
| Mi->Ma | MPF activation | Mass Action | kc*Mi |
| Ca->Ci | Cdc25 inactivation | Michaelis-Menten | (vcp _{pp} _ |
| Ci->Ca | Cdc25 activation | Michaelis-Menten | (vc_*Ci* |
| Wa->Wi | Wee1 inactivation | Michaelis-Menten | (vw_*Wa |
| Wi->Wa | Wee1 activation | Michaelis-Menten | (vw_*vw |
| L-> | Labelled inactive MPF affected by Cdc25 | Mass Action | kc*L |
| ->L2 | Labelled inactive MPF affected by Wee1 | Local | kw*(1-L |
| kc | | Species | vcp*Ci+ |
| kw | | Species | vw*Wi+ |
| vcp_ | | Species | vcp*Cdc |
| vcpp_ | | Species | vcpp*Cd |
| vcppp_ | | Species | vcppp/C |
| wvp_ | | Species | wvp*We |
| wvpp_ | | Species | wvpp*W |
| wvppp_ | | Species | wvppp/M |
| kmc_ | | Species | kmc/Cdc |
| kmcr_ | | Species | kmcr/Cd |
| kmw_ | | Species | kmw/We |
| kmwr_ | | Species | kmwr/W |
| vc_ | | Species | vc*Cdc2 |
| vw_ | | Species | vw*Cdc2 |
| Cdc25Total_ | | Species | Cdc25T |

JigCell

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SBML Model Integration Server

A web interface to the SBML_odeSolver pro

This server will integrate a valide SBML model.
At this stage the web service is experimental!!!

Instructions

- Please upload a **valid SBML Model**
- Please provide a **valid email address** (you will be notified by email)
- Your model will be validated prior to integration using the function
- If **validation errors** occur, please correct them and resubmit your

no file selected

Your Email Address

Simulation Time (use scientific notation e.g. 1e7 for 10000000)

Print Step

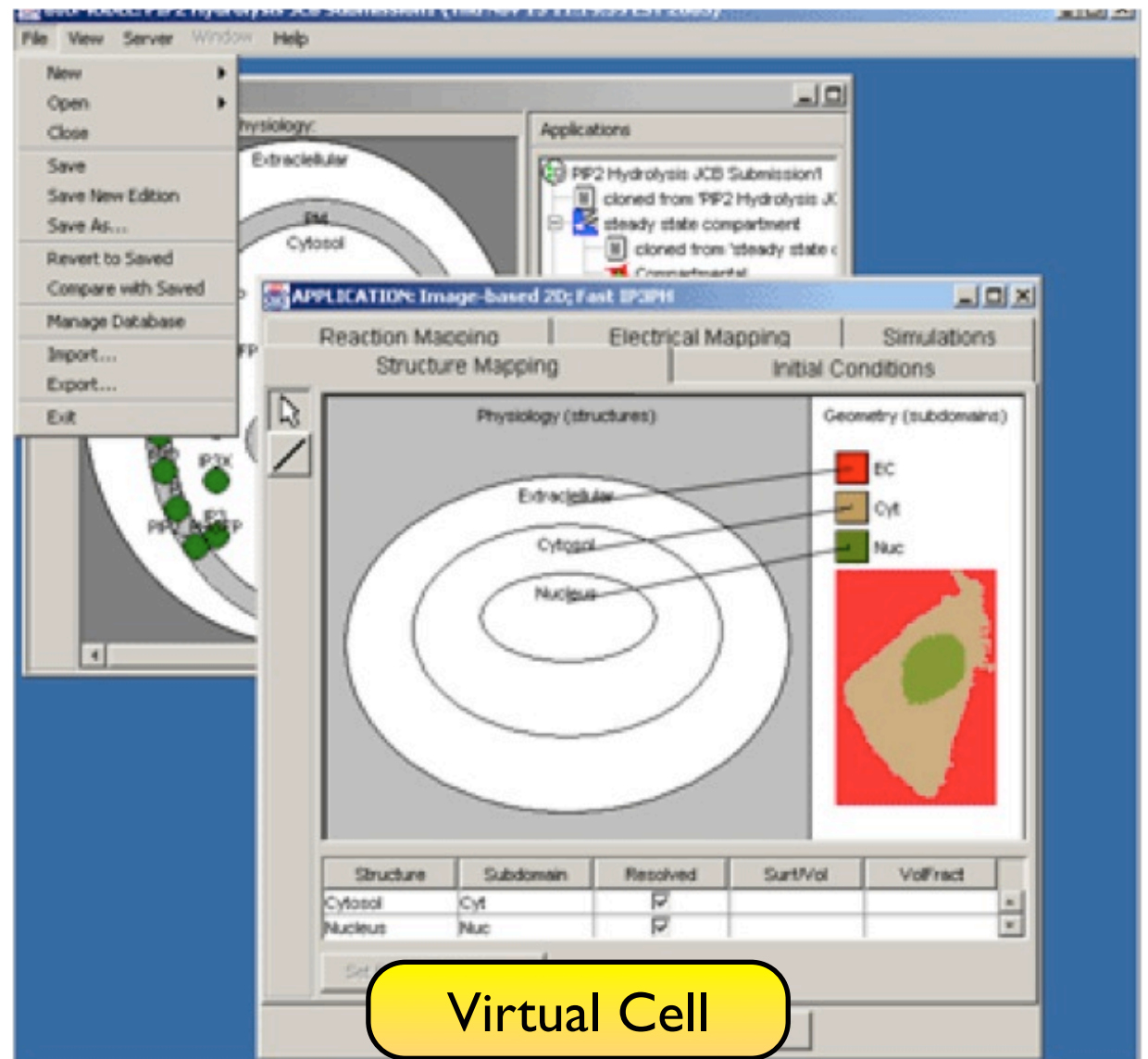
Absolute Error

Relative Error

SBML ODE Solver

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Many common types of model representation frameworks

- ▶ (Continuous) nonlinear differential equations
- ▶ (Discrete) stochastic systems
- ▶ Boolean networks
- ▶ Bayesian networks
- ▶ Petri Nets
- ▶ others...

Ability to exchange models is critical

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- ▶ Simply publishing equations is not enough
 - ▶ Don't want to transcribe equations from papers
 - ▶ You want a common file format

Ability to exchange models is critical

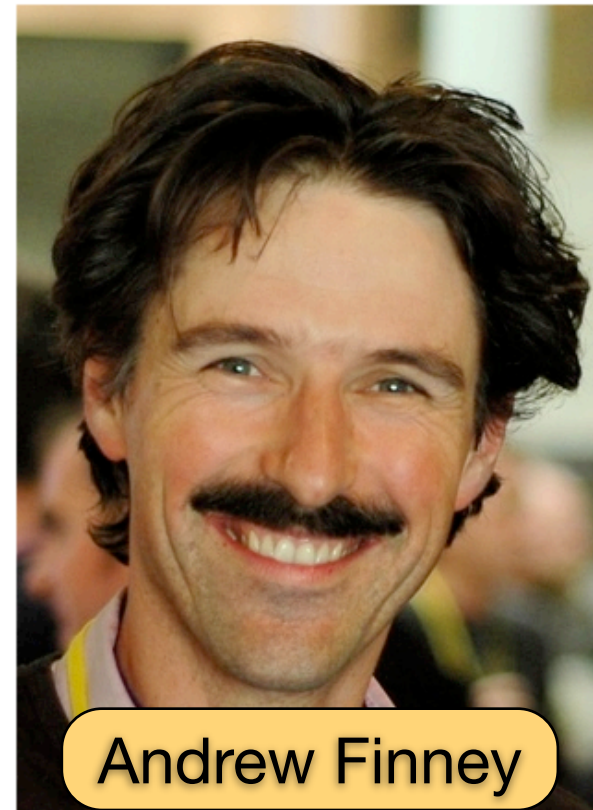
- ▶ Simply publishing equations is not enough
 - ▶ Don't want to transcribe equations from papers
 - ▶ You want a common file format
- ▶ **Not** a new idea—seems obvious
 - ▶ Still, a format hadn't existed before year 2000
 - ▶ Each tool had its own unique proprietary format
 - ▶ (Fewer tools too)



Hiroaki Kitano



John Doyle



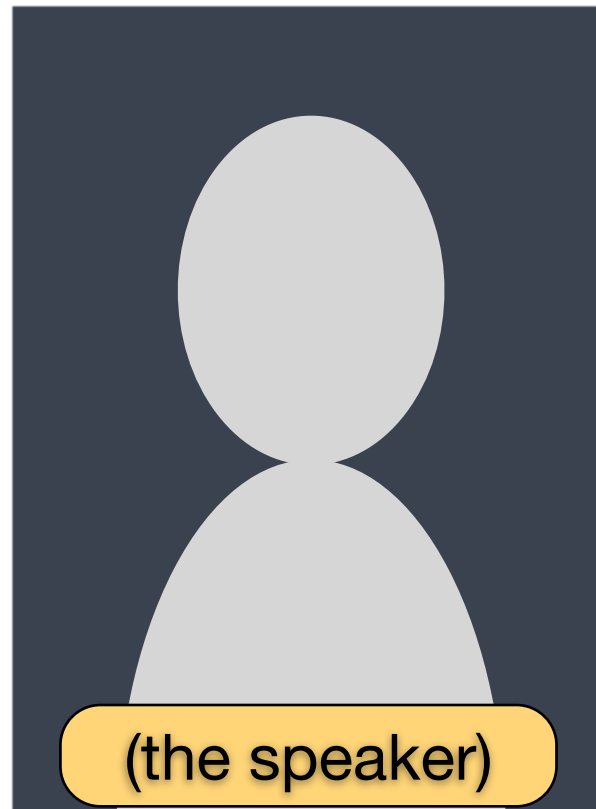
Andrew Finney



Herbert Sauro



Hamid Bolouri



(the speaker)

JST ERATO Kitano Project

One initial component: get 8–
10 software systems interacting

SBML = Systems Biology Markup Language

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- ▶ Machine-readable format for computational models

SBML = Systems Biology Markup Language

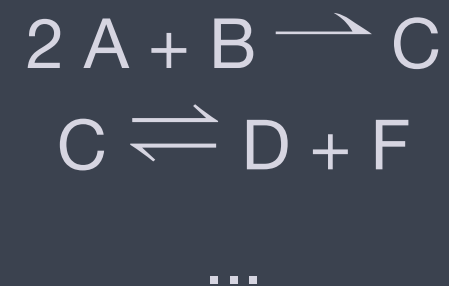
- ▶ Machine-readable format for computational models
- ▶ Suitable for reaction networks
 - ▶ Arbitrary rate functions



...

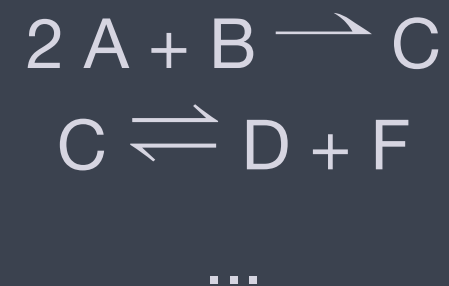
SBML = Systems Biology Markup Language

- ▶ Machine-readable format for computational models
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 - ▶ Arbitrary rate functions
- ▶ Models can also include
 - ▶ Compartments
 - ▶ Mathematical “extras”



SBML = Systems Biology Markup Language

- ▶ Machine-readable format for computational models
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- ▶ Models can also include
 - ▶ Compartments
 - ▶ Mathematical “extras”
- ▶ Declarative, not procedural




SBML is an XML format

- ▶ SBML defined using UML and XML Schema
- ▶ Targeted at XML, but mostly independent of it
- ▶ A **lingua franca** for software, not humans
- ▶ Think HTML

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="1"
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      <assignmentRule variable="S1">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
          <apply>
            <divide/>
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```


9

Now the *de facto* standard



SBML.org - The home site for the Systems Biology Markup Language

http://sbml.org/index.psp

SBML Systems Biology Markup Language

home • contacts • documents • downloads • FAQs • forums • Level 3 • models

The Systems Biology Markup Language (SBML) is a computer-readable format for representing **models of biochemical reaction networks**. SBML is applicable to metabolic networks, cell signaling pathways, regulatory networks, and many others.

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 100 software systems**, including the following (where "*" indicates SBML support in development):

| | | | |
|---------------------|---------------------|-----------------|-------------|
| BALSA | DBsolve | MMT2 | SBMLmerge |
| BASIS | Dizzy | Modesto | SBMLR |
| BIOCHAM | E-CELL | Molecularizer | SBMLSim |
| BioCharon | ecellJ | Monod | SBMLToolbox |
| ByoDyn | ESS | Narrator | SBLID |
| BioCyc | FluxAnalyzer | NetBuilder | SBToolbox |
| BioGrid | Fluxor | Oscill8 | SBW |
| BioModels | Gepasi | PANTHER Pathway | SClpath |
| BioNetGen | Gillespie2 | PathArt | Sigmoid* |
| BioPathway Explorer | HSMB | PathScout | SigPath |
| Bio Sketch Pad | HybridSBML | PathwayLab | SigTran |
| BioScape | INSII ICG discovery | Pathway Tools | SIMBA |

- ▶ Supported by >100 systems
- ▶ Accepted by journals
 - ▶ Nature
 - ▶ PLoS
 - ▶ BMC
- ▶ Used in textbooks & courses

A community of modelers and software developers

- ▶ **sbml-discuss** (275+ people), **sbml-announce**
- ▶ Annual **SBML Forum** meeting (at ICSB)
- ▶ Annual **SBML Hackathon**

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Support by SBML Team

- ▶ Writing grants for core development
- ▶ Writing infrastructure software
 - ▶ libSBML
 - ▶ MathSBML, SBMLToolbox
- ▶ Maintaining web & mailing list resources
- ▶ Organizing workshops & other events

Latest: SBML Level 2 Version 2

► Final version released
September 26

Systems Biology Markup Language (SBML) Level 2: Structures and Facilities for Model Definitions

Andrew Finney
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Magdalen Centre
Oxford Science Park
Oxford, OX4 4GA, UK

Michael Hucka
mhucka@sbml.org
Biological Network Modeling Center
Beckman Institute, Mail Code 139-74
California Institute of Technology
Pasadena, CA 91125, USA

Nicolas Le Novère
lenov@ebi.ac.uk
European Bioinformatics Institute
Wellcome Trust Genome Campus, Hinxton
Cambridge, CB10 1SD, UK

SBML Level 2, Version 2, Revision 1
26 September 2006

Corrections and other revisions of this SBML language specification may appear over time.
Notifications of revisions are broadcast on the mailing list sbml-announce@caltech.edu

The latest revision of the SBML Level 2 Version 2 specification is available at
<http://sbml.org/specifications/sbml-level-2/version-2/>

This revision of the SBML Level 2 Version 2 specification is available at
<http://sbml.org/specifications/sbml-level-2/version-2/revision-1/>

Examples of significant changes

- ▶ Many clarifications
- ▶ Simplification to the unit system
- ▶ Addition of species types, compartment types
- ▶ Addition of “constraints”
- ▶ Support for the Systems Biology Ontology (SBO)
- ▶ Recommended standard format for annotations
- ▶ “Revisions” process for handling errata



What lies ahead?

Revised SBML governance & development process

- ▶ Borrow ideas from W3C & other organizations
- ▶ Implement a better-defined, **regimented process**
 - ▶ Calls for proposals, etc.
 - ▶ Voting, etc.
- ▶ Have an **architectural board** to steer development
- ▶ Have **more SBML Editors**
 - ▶ Elect SBML Editors for **limited terms**

SBML Level 3

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- ▶ Modular language extensions
 - ▶ Core expected to be based “mostly” on Level 2 Version 2

SBML Level 3

- ▶ Modular language extensions
 - ▶ Core expected to be based “mostly” on Level 2 Version 2
- ▶ Layered on top of core: feature sets for—
 - ▶ Diagram storage
 - ▶ Multicomponent species
 - ▶ Models composed of submodels
 - ▶ Arrays and/or sets of components
 - ▶ Spatial geometry
 - ▶ *Other capabilities*

Full SBML Test Suite

- ▶ Allows developers to test implementation of SBML support
- ▶ Critical for improving software interoperability
- ▶ Currently have a partial “SBML semantic test suite”
- ▶ Needs further work to—
 - ▶ Complete coverage of SBML features
 - ▶ Improve ease of use
 - ▶ Update for Level 2 Version 2 and Level 3
 - ▶ Add web system for reporting results, comparisons, etc.



BioModels.net

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unregulated

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unregulated

low info content

BioModels.net consortium

- ▶ International collaboration to develop:
 1. A public database of **curated, annotated** models: **BioModels Database**
 2. Guidelines for curation and annotation of models: **MIRIAM**
 3. Ontology suited to computational models: **SBO**
- ▶ Main collaborators
 - ▶ Nicolas Le Novère's Computational Neurobiology group at EBI (UK)
 - ▶ Hucka and SBML Team at Caltech (USA) and U. Hertfordshire (UK)
 - ▶ Herbert Sauro's group at Keck Graduate Institute
 - ▶ Hans Westerhoff & Jacky Snoep's JWS Online (ZA and UK)
 - ▶ Hiroaki Kitano's Systems Biology Institute

BioModels Database

<http://www.ebi.ac.uk/biomodels>

- ▶ Stores & serves **quantitative** models of bio. interest
 - ▶ **Free, public** resource
 - ▶ Models must be described in **peer-reviewed** publication(s)
- ▶ Imports models in **SBML** & **CellML** formats
 - ▶ Exports in **SBML**, **CellML**, **SciLab**, **XPP** and **BioPAX**

The screenshot displays the BioModels Database interface. At the top, the URL <http://www.ebi.ac.uk/compneur-srv/biomodels-main/publ-model.do?mid> is visible in the browser's address bar. The page features the EMBL-EBI logo and a navigation menu with links like 'Home', 'About EBI', 'Groups', 'Services', 'Toolbox', and 'Databases'. The main content area shows a model entry for 'BIOMD0000000005 Tyson1991_CellCyc'. Below the model ID, there are links for 'SBML L2 V1', 'CellML', 'SciLab', 'XPP', and 'BioPAX'. Further down, there are links for 'View Model Graph', 'View Model SVG', 'View Simulation Result', and 'View Model Details'. A 'Submit Model Comment/Bug' link is also present. At the bottom, a 'Reference Publication' section is visible, showing the 'Publication ID: 1831270' and the title 'Proc Natl Acad Sci U S A. Modeling the cell division cycle of the fission yeast Schizosaccharomyces pombe. Tyson JJ. Department of Biology, University of California, San Diego, La Jolla, CA 92037, USA.'

Models are curated

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- ▶ Human curators check correspondence to publication

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 - ▶ General info about model, author, publication, etc.
 - ▶ References to external data resources: UniProt, KEGG, NCBI, Gene Ontology, ChEBI, BIND, Reactome



Features of BioModels Database

- ▶ **True database:** can search model content & annotations
 - ▶ SBML XML stored in XINDICE; annotations in an SQL database
- ▶ Some statistics today (6th release in Oct. 2006):
 - ▶ **70+ curated, dynamical models**
 - ▶ E.g.: Tyson yeast cell cycle models, Elowitz E. coli repressilator, Teusink et al. yeast glycolysis, Rohwer et al. E. coli glucose transport
 - ▶ 26 non-curated models (e.g., models lacking kinetics, such as FBA)
- ▶ Model sources: us, Nature/EMBO ***Molecular Systems Biology***, repositories such as JWS Online and CellML, individual researchers

MIRIAM

- ▶ “Minimal info. requested in the annotation of biochemical models”
- ▶ Proposed guidelines for basic annotation of models
 - ▶ **Reference correspondence**, e.g.,
 - ▶ Be encoded in a public, standardized format (SBML, CellML, etc.)
 - ▶ Must be instantiated in a simulation & all quantitative attributes defined
 - ▶ **Attribution annotation** (info about model creators, source reference, etc.)
 - ▶ **External source annotations** (linking model element to data source)
- ▶ Goal: minimal common standards enabling sharing of curation effort

SBO = Systems Biology Ontology

- ▶ Occupies a space not filled by other ontologies
 - ▶ Primarily for describing rate laws and constituents
 - ▶ **Classification of rate laws**
 - ▶ Each term includes a mathematical function definition
 - ▶ Controlled vocabulary for the **roles of reaction participants**
 - ▶ E.g.: “substrate”, “catalyst”, “competitive inhibitor”, etc.
 - ▶ Controlled vocabulary for the **roles of parameters** in quantitative models

BioModels.net portal

The image shows a collage of three web browser windows. The leftmost window displays the BioModels.net homepage, featuring a large 'BION' graphic and text about the project's goals. The middle window shows the EMBL-EBI SBO Ontology Browser, displaying a hierarchical tree of the Systems Biology Ontology (SBO) with categories like 'quantitative parameter', 'participant role', and 'reactant'. The rightmost window shows the EMBL-EBI homepage, highlighting the BioModels database and providing links to curated models, search, and model submission.

BioModels.net

http://biomodels.net/

WoS Finance News (1820)

BION

Home | Contacts | Database

The Next Step After Standard

For computational modeling to become a reality, researchers must be able to exchange and share common model representation formats, allowing researchers to exchange and share data with accuracy.

The BioModels.net project is another step towards (1) defining standards for model curation, (2) developing connections to biological data resources, and (3) creating an accessible database of annotated, curated models in various formats.

Helping to Define Community

EMBL-EBI
European Bioinformatics Institute

EBI Home About EBI Groups Services Tools

SBO Ontology Browser

SBO::Systems Biology Ontology

☐ Refresh tree

☒ **sbo**

- ☒ **quantitative parameter**
- ☒ **participant role**
- ☒ **reactant**

BioModels

A Database

BioModels Database search and retrieval interests. Models linked to relevant pathways, control

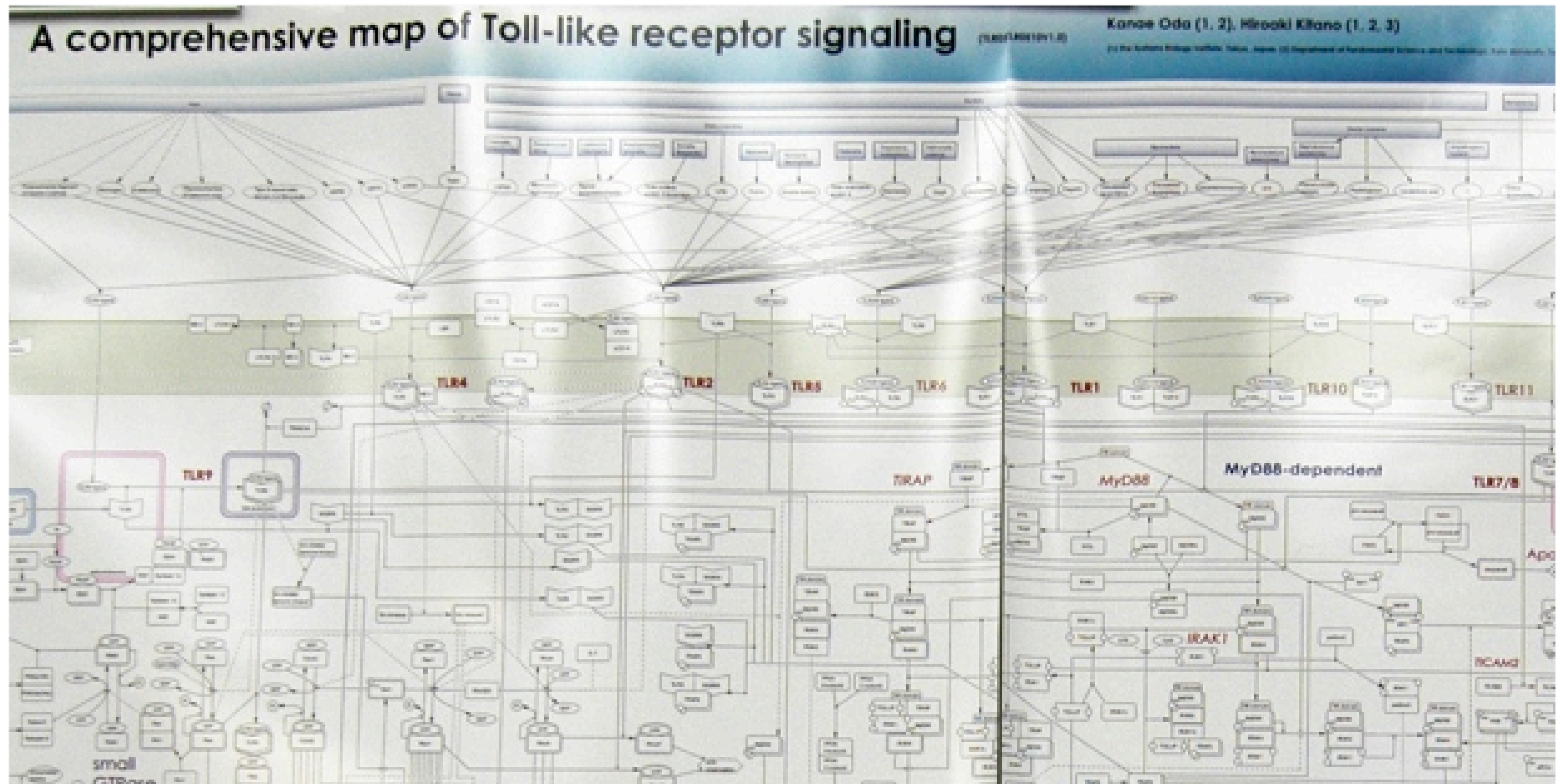
Submit Your Model

- Curated Models
- Non-curated Models
- Search

Curation tips

Annotation tips

[Browse curated]



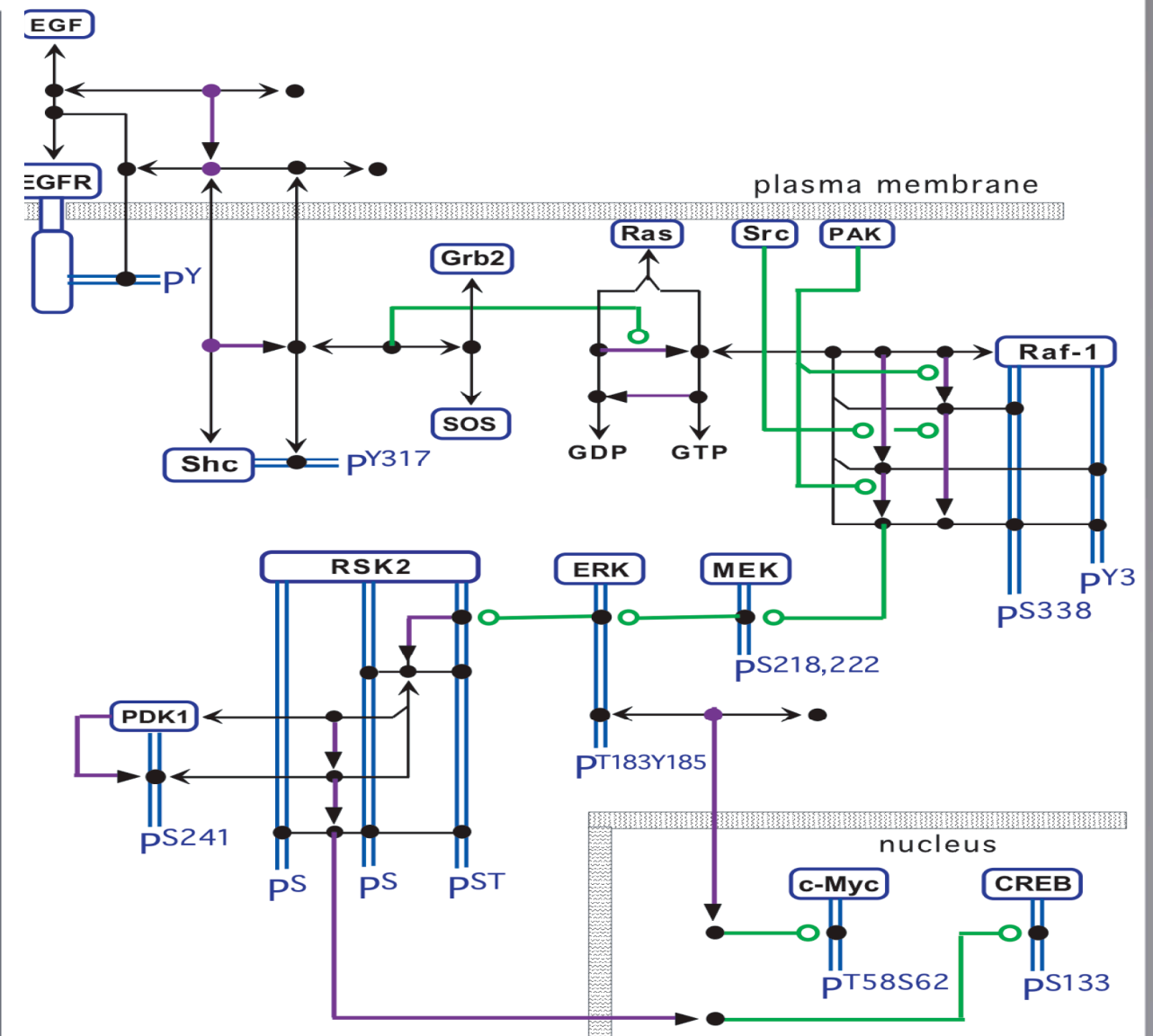
SBGN

Background

- ▶ No current standard for network diagrams in biology
- ▶ No consistency—
 - ▶ Between authors
 - ▶ Between papers
 - ▶ Between publications

Background

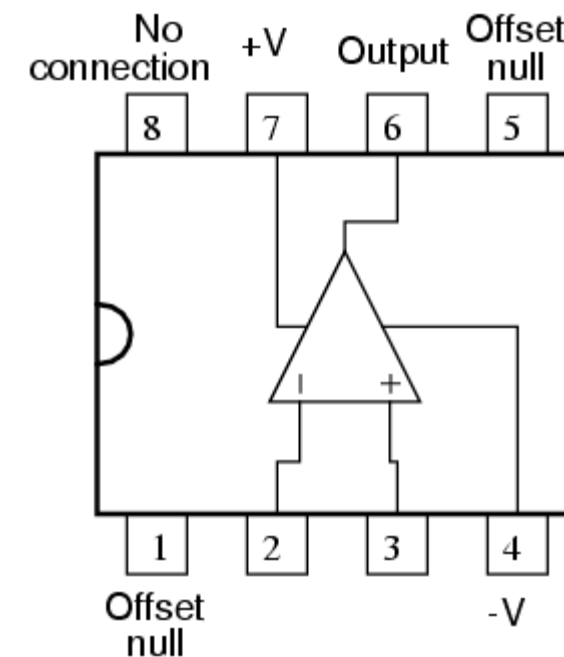
- ▶ No current standard for network diagrams in biology
- ▶ No consistency—
 - ▶ Between authors
 - ▶ Between papers
 - ▶ Between publications



Standardization would bring benefits

- ▶ Notations standardized in electrical/electronics, software engineering, etc.
- ▶ Taught in textbooks
- ▶ Supported by software
 - ▶ Automated verification
- ▶ Consistency makes it easier to read new diagrams

Typical 8-pin "DIP" op-amp integrated circuit



SBGN = Systems Biology Graphical Notation

- ▶ Goal: bring simulation/modeling community together and develop a proposal for a standard notation for **some** types of diagrams
 - ▶ Starting with metabolic & signaling networks
- ▶ Begun late '05 by Kitano/Le Novère/Hucka thanks to NEDO funding
- ▶ 2 SBGN workshops held so far (Feb and Oct 2006)
 - ▶ Many groups participating: Goryanin group (U. Edinburgh), BioPAX (MSKCC New York), SRI, CellML, EML (Germany), many others
 - ▶ Join if you're interested!
- ▶ Currently working towards a first proposal



Closing

The funding

- ▶ National Institute of General Medical Sciences (USA)
- ▶ JST ERATO Kitano Symbiotic Systems Project (Japan) (to 2003)
- ▶ National Science Foundation (USA)
- ▶ International Joint Research Program of NEDO (Japan)
- ▶ JST ERATO-SORST Program (Japan)
- ▶ Japanese Ministry of Agriculture
- ▶ Japanese Ministry of Educ., Culture, Sports, Science and Tech.
- ▶ BBSRC e-Science Initiative (UK)
- ▶ DARPA IPTO Bio-SPICE Bio-Computation Program (USA)
- ▶ Air Force Office of Scientific Research (USA)
- ▶ STRI, University of Hertfordshire (UK)
- ▶ Beckman Institute, Caltech (USA)

| SBML Team | BioModels DB Team | SBGN Team |
|----------------------|--------------------------|--------------------------|
| Michael Hucka | Nicolas Le Novère | Hiroaki Kitano |
| Andrew Finney | Chen Li | Nicolas Le Novère |
| Ben Bornstein | Mélanie Courtot | Michael Hucka |
| Sarah Keating | Lu Li | Akira Funahashi |
| Bruce Shapiro | Camille Laibe | |
| Ben Kovitz | Nicolas Rodriguez | |
| Hamid Bolouri | Harish Dharuri | |
| Herbert Sauro | Marco Donizelli | |
| Maria Schilstra | Alexander Broicher | |
| Jo Matthews | Arnaud Henry | |

A million thanks to the SBML Community too

Where to learn more

- ▶ <http://sbml.org>
- ▶ <http://biomodels.net>
- ▶ <http://sbgn.org>
- ▶ *Upcoming:*
 - ▶ BioModels.net Training Camp 2007 January 13-15, Manchester, UK
 - ▶ SBML Hackathon 2007 in June at U. Newcastle, UK
 - ▶ SBGN Workshop in 2007 (probably March 2007, Gosau, Austria)
 - ▶ SBML Forum 2007 in Long Beach, CA, USA, Oct. 5-6 (ICSB 2007)
- ▶ **Thank you!**